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Reactivation of Herpes Virus under Fingolimod – a Case of Severe Herpes Simplex Encephalitis

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Fingolimod (FTY720, Gilenya®, Novartis Pharma AG, Basel, Switzerland) is a sphingosin-1-phosphate (S1P) receptor modulator with immunomodulatory properties, which traps naïve and central memory T cells in lymph nodes leading to reduced numbers of peripheral blood lymphocytes, and is the first licensed oral drug for multiple sclerosis (MS) (1, 2). We here report a case of a near fatal herpes simplex virus 1 (HSV-1) encephalitis under the licensed dose of fingolimod in a MS patient.

A 38 year-old male was diagnosed with relapsing-remitting MS in 2007. In 2007 he entered the TRANSFORMS phase 3 study comparing fingolimod (0.5 or 1.5mg daily) with with interferon beta 1a (Avonex®, Biogen Idec, Cambridge, USA) and placebo. Since 08/2008 he participated in the TRANSFORMS extension study and received fingolimod (1.25 or 0.5mg) and from 04/2010 he continued with 0.5mg (Umbrella). In 03/2013, he had minor deficits with an EDSS (expanded disability status score(3)) of 2.5 (which ranges from 0 to 10, with higher scores indicating greater disability and 10 = death from MS). From 2007 – 2013 the patient suffered only from one MS relapse and showed EDSS worsening from 1.5 – 2.5.

In 04/2014, he was admitted to the emergency department with loss of consciousness, fever and epileptic seizures. Cranial computed tomography (CT) showed a hypodense area in the right temporal lobe (figure 1A). Diagnosis of HSV-1 encephalitis was made by PCR from cerebrospinal fluid (CSF) showing 216.721 HSV-1 DNA copies/ml, 10 cells/µl and total protein of 0.519 g/l. Blood count showed lymphopenia of 410 cells/µl. Anti-HSV-1 IgG antibodies were already positive at presentation in serum and CSF, while anti-HSV-1 IgM and ani-HSV-2 antibodies remained negative. The medical history mentioned a previous herpes labialis. Antiviral therapy with intravenous aciclovir was initiated immediately at the day of presentation at the standard dose. Cranial magnetic resonance imaging (MRI) showed signs of non-hemorrhagic encephalitis of archecortical areas of both hemispheres (figure 1B).

After 34 days, the patient was referred to a neurological rehabilitation center. At discharge he was alert, showed signs of right dominant tetraparesis and was unable to speak due to a tracheal cannula, resulting in an EDSS of 9.5 indicating severe disability. Follow-up examinations in the next 9 months showed clinical worsening and progressive brain atrophy accentuated in the post-encephalitic regions (figures 1C and 1D).

Despite its potent immunomodulatory effects leading to reduced circulating lymphocyte counts fingolimod did not lead to increased rates of severe infections in clinical phase 3 studies (1, 2, 4). Only immunity against herpes viruses with CNS latency, especially varicella zoster virus (VZV) and HSV, shows subtle impairments. This has been shown by two cases, who died from fatal infections during 1.25mg fingolimod and additional course of

corticosteroids for MS relapse treatment in one phase 3 study (2). Furthermore, a second phase 3 study showed an increased rate of VZV infections (4), whereas no increase in herpes virus infections was seen in a third phase 3 study (1). Our patient had not received corticosteroids or other immunomodulatory treatments apart from fingolimod, the only co-medication was buproprion, Wellbutrin®, GlaxoSmithKline AG, Münchenbuchsee, Switzerland and occasionally methylphenidate (Ritalin®, Novartis Pharma AG, Basel, Switzerland). Prior to onset of HSV-1 encephalitis he had not shown any evidence for immunologically relevant co-morbidities during continuous follow-up in our MS outpatient clinic since 2007. Beside these rare and fatal cases a recent study reported that fingolimod treatment of MS patients lowers VZV-specific immunity and suggested that subclinical VZV reactivation, demonstrated by PCR detection of VZV DNA in the saliva, is higher among patients treated with fingolimod compared with healthy controls (5).

Different from other immunomodulatory drugs that can compromise specific aspects of immune control fingolimod treatment may lead to a subtle, but in some cases clinically relevant compromise of immune responses against herpes viruses that stay in their latent stages in the nervous system compartment, i.e. VZV and HSV-1, while immune responses against those that reside in immune organs (CMV and EBV) appear unaffected. In order to try to avoid serious adverse events it will be important to understand these interactions better.

By reporting this case of HSV-1 encephalitis under 0.5mg fingolimod we want to stress the importance of further studies on how fingolimod impairs immunity against HSV-1 and VZV to prevent such severe complications in the future.

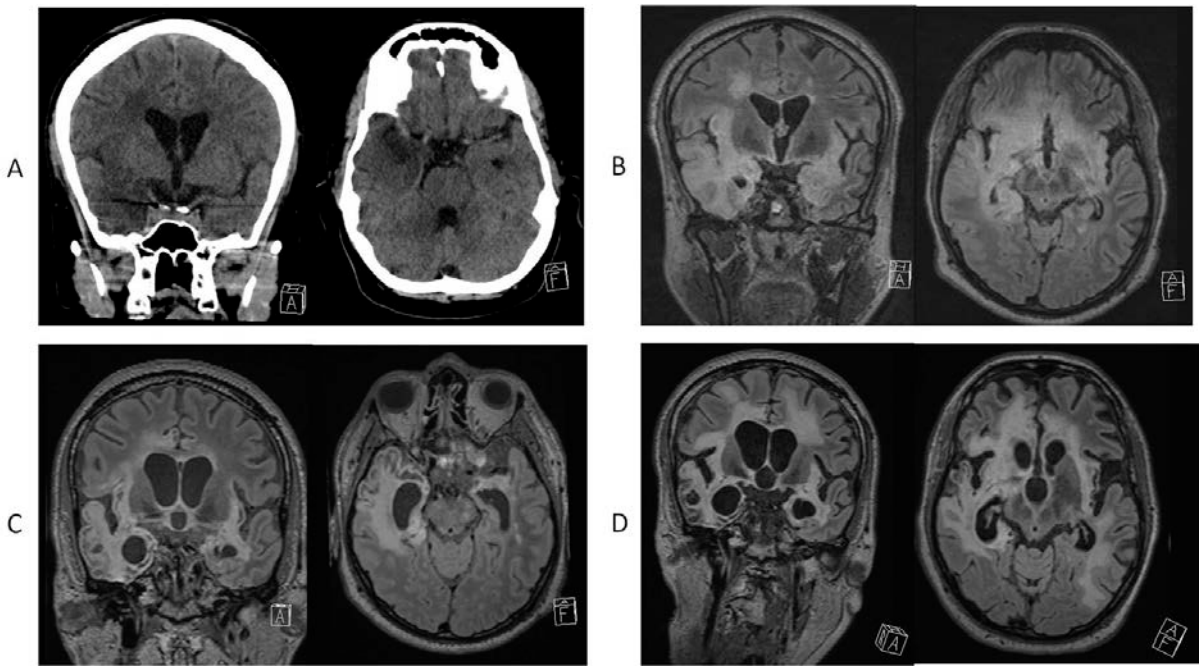

Figure Legend 1: Neuroimaging

A: Cranial CT scan at the day of admission (coronarl, left, and axial slices, right) shows a hypodense area of the right temporal lobe.

B: MRI scan of the brain (coronarl slices left, axial slices right, depicted are FLAIR sequences) shows hypodense areas of archecortical structures and the right temporal lobe. The follow-up MRI scans 4 months (C) and 9 months (D) show progressive and wide-spread leukencephalopathy. Depicted are coronal (left) and axial (right) slices of FLAIR sequences. The positioning of the head the scanner differs, partially related to agitation of the patient during the examination. All scans are performed and kindly provided by the Department of Neuroradiology, University Hospital Zurich, Switzerland.

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